PATENT COOPERATION TREATY

Bee
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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

RAMBELLI, Paolo
Jacobacci & Partners SpA
Corso Emilia 8
I-10152 Torino
ITALIE

RICEVUTO
10. NOV. 2005

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.11.2005
Applicant's or agent's file reference PC503PR ✓	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/006330 ✓	11.06.2004 ✓	13.06.2003 ✓

Applicant
LABORATORIOS S.A.L.V.A.T., S.A. et al. ✓

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel. +49 89 2399-8031

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC503PR ✓	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/006330 ✓	International filing date *(day/month/year)* 11.06.2004 ✓	Priority date *(day/month/year)* 13.06.2003 ✓

International Patent Classification (IPC) or national classification and IPC

C07C235/52, C07D333/08, C07D209/04, C07D241/40, C07D213/02, A61K31/166, A61K31/381, A61K31/404, A61K31/498, A61K31/435, A61P5/00

Applicant

LABORATORIOS S.A.L.V.A.T., S.A. et al. ✓

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 21 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.04.2005	08.11.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Goetz, G

Telephone No. +49 89 2399-8105

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006330

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-4, 7, 9, 10, 12-16, 19-83, 85-90	as originally filed ✓
5, 5a, 6, 8, 11, 17, 18, 84	received on 15.04.2005 with letter of 13.04.2005 ✓

Claims, Numbers

9-38	as originally filed ✓
1-8	received on 15.04.2005 with letter of 13.04.2005 ✓

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 30-38

because:

☒ the said international application, or the said claims Nos. 30-38 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-38
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-.29
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

D1: WO 00/55118 A (GLAXO GROUP LTD ; BLANCHARD STEVEN GERARD (US); COBB JEFFERY EDMUND (U) 21 September 2000 (2000-09-21)

D2: WO 97/27847 A (PATCHETT ARTHUR A ; BERGER JOEL P (US); MERCK & CO INC (US); MOLLER DA) 7 August 1997 (1997-08-07)

1. For the assessment of the present claims 30 to 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

   Claims 30 - 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Following amendments are considered to go beyond the disclosure as originally filed (Article 34(2)(b) PCT:

   Definition of -I'- :

   The added substituents "phenyl", "phenoxy" and "benzyloxy" have their basis only in the examples, where other variables have a certain specific definition. Any generalization of the examples is considered to represent an amendment which violates the requirements of Article 34(2)(b) PCT.

   Definition of R6 and R7:

   Basis for this amendment is to be found only in examples 36 and 251. Any generalization of the examples is considered to represent an amendment which violates the requirements of Article 34(2)(b) PCT.

   The present International Preliminary Examination Report is thus based on claim 1 as originally filed.

3. The claimed compounds differ from the compounds disclosed in D1 by the fact that in D1 the phenyl-ring of the benzamid-group is substituted by a nitro group and a group "X" whereas the claimed compounds do not have such a substitution pattern.
The claimed compounds differ from the compounds disclosed in D2 by the fact that D2 does not disclose benzamid-derivatives.
The subject matter of present claims 1 to 38 is thus considered to be novel over said prior art (PCT Article 33.2).

4. In view of D1 which is considered to represent the closest prior art the underlying problem can be defined by the provision of further compounds acting as modulators of PPAR-gamma.
To represent a solution it has to be shown that a representative amount of compounds falling within the scope of present formula (I) but showing different structural features show this activity. In particular a representative number of benzamides falling within the structure of formula (I) but having different substitution pattern have to be tested and proven for their activity.
Having regard to the data provided by the Applicant (see Annex I) it can be considered that the underlying problem has been solved over the whole scope of the general formula (I) of claim 1.
This solution is in addition considered to be based on an inventive step: starting from D1 as the closest prior art document it was not obvious for the skilled person to modify the basic structure of the compounds of D1 in the way it has been done in present application to still get biological active modulators of PPAR-gamma.

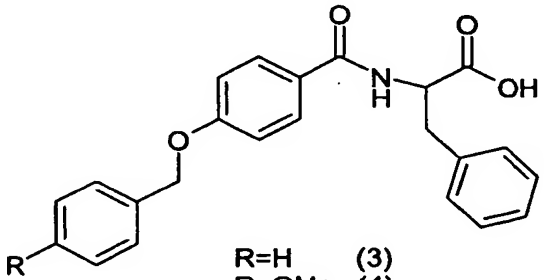
   Consequently present claims 1 to 38 are considered to be based on an inventive step (PCT Article 33.3).

5. Industrial applicability is given for present claims 1 to 29 (PCT Article 33.3).

discovery of drugs that have great potential in the treatment of diseases such as type-2 diabetes, dyslipidemia, syndrome X, cardiovascular diseases (including atherosclerosis), hypercholesteremia, colon cancer, skin disorders (including psoriasis, and wound healing, Tan *et al.*, *Expert Opin. Ther. Targets*, **2004**, *8*, 39), and bone diseases (Pei *et al.*, *J. Clin. Invest.*, **2004**, *113*, 805-806).

Consequently, it is of great interest to provide new therapeutic agents that selectively modulate PPARγ, and PPARγ / PPARδ.

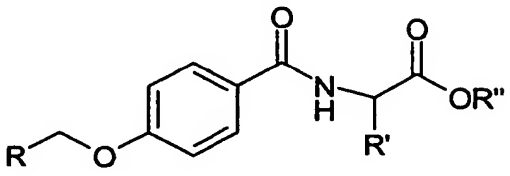
Kundu and collaborators have described benzamides (3), (4) and (5) as *N*-□-glucosidase inhibitors (*Comb. Chem. High.* **2002**, *5*, 545-550). These compounds are structurally close to those of this invention, but were described for different uses.



R=H (3)
R=OMe (4)
R=Br (5)

Kundu and collaborators have described benzamides (3), (4) and (5) as N-□-glucosidase inhibitors (Comb. Chem. High. **2002**, 5, 545-550). WO 02/096426 disclose compounds (6) and (7) as intermediates for compounds which are matrix metalloproteinase inhibitors. Finally, WO 04/014844 disclose compounds (8) and (9) as factor IX modulators. These

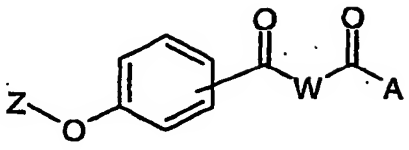
compounds are structurally close to those of this invention, but were described for different uses.



	R	R'	R''
(3)	Phenyl-	Benzyl-	-H
(4)	4-Methoxyphenyl-	Benzyl-	-H
(5)	4-Bromophenyl-	Benzyl-	-H
(6)	2-Methylquinolin-4-yl-	Cyclopentyl-	-methyl
(7)	2-Methylquinolin-4-yl-	Tetrahydropyran-4-yl-	-methyl
(8)	Phenyl-	Biphenyl-4-ylmethyl	-H
(9)	Phenyl-	4'-Trifluoromethoxybiphenyl-4-methyl-	-H

SUMMARY OF THE INVENTION

One aspect of the present invention relates to the provision of new compounds of formula (I),



(I)

its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein the central benzene ring may be substituted in *meta*- or *para*-position and,

-A is a radical selected from the group consisting of -OR1, -NR2OR1 and -NR2R3; wherein R1, R2 and R3 independently represent -H or -(C_1-C_4)-alkyl;

-W- is a biradical selected from the group: -NH-CH(E)-, ~~-N(E)-CH$_2$-~~, and -N(D)-CH_2-CH_2-; wherein E is a radical of the -G-I-J-K type and D is a radical of the -G-I'-J-K type where:

-G - is a bond or a -$(CH_2)_{1-4}$- biradical;

-I - is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -

being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-J- is a bond or a biradical selected from the following groups:

a) -$(CH_2)_{1-4}$-alkylidene;

b) -O-, ~~-S-, -SO-, $-SO_2$-, -CO-, -OCO-, -COO-, -OCONR2-, -NR2COO-, -CONR2-, -NR2CO-, -NR2-, -NR2SO_2-, -SO_2NR2-,~~ and

c) -O-(C_1-C_4)-, ~~-(C_1-C_4)-O-, -S-(C_1-C_4)-, -(C_1-C_4)-S-~~, -SO-(C_1-C_4)-, -(C_1-C_4)-SO-, -SO_2-(C_1-C_4)-, -(C_1-C_4)-SO_2-, -OCO-(C_1-C_4)-, -COO-(C_1-C_4)-, -(C_1-C_4)-OCO-, -(C_1-C_4)-COO-, -OCONR2-(C_1-C_4)-, -NR2COO-(C_1-C_4)-, -(C_1-C_4)-OCONR2-, -(C_1-C_4)-NR2COO-, -CONR2-(C_1-C_4)-, -NR2CO-(C_1-C_4)-, -(C_1-C_4)-CONR2-, -(C_1-C_4)-NR2CO-, -NR2-(C_1-C_4)-, -(C_1-C_4)-NR2-, -SO_2NR2-(C_1-C_4)-, -NR2SO_2-(C_1-C_4)-, ~~-(C_1-C_4)-SO_2NR2-, -(C_1-C_4)-NR2SO_2-;~~

-K is a radical selected from the following groups:

a) -H;

b) (C_1-C_4)-alkyl;

c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all

c) benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F, phenyl, phenoxy and benzyloxy;

-Z is a radical selected from the following groups:

a) -Q-I-J-T wherein

-Q- is a biradical $-(CH_2)_{1-3}-$;

-I- is as defined above;

-J- is as defined above; and

optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

c.e) a heterocycle and heterocycle-(C_1-C_3)-alkyl, wherein the heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocyclo optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or severalseveral -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is as defined above;

-I- is as defined above;

-J- is as defined above; and

-T is as defined above;

d) -(CH_2)$_s$-NR6R7, wherein s is as defined above, and R6 and R7 together with the N are joined forming a five-, ~~or~~ six-~~membered~~ or seven-membered cycle optionally containing from one to three additional heteroatoms selected from O, S and

N, and that may be fused or substituted by one or two five- or six-membered cycles optionally containing one or several heteroatoms selected from the group composed of O, S and N, all the cycles being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

e) $-(CH_2)_u$-CO-NR6R7 wherein u is as defined above, and R6 and R7 are as defined above;

with the proviso that compound of formula (I) is neither of 2-(4-benzyloxybenzoylamino)-3-phenylpropionic acid, nor 2-[4-(4-methoxybenzyloxy)benzoylamino]-3-phenylpropionic acid, nor 2-[4-(4-bromobenzyloxy)benzoylamino]-3-phenylpropionic acid,

insert <-> from page 103.

In a particular embodiment of this aspect of the invention, in the compounds of formula (I), -W- is -NH-CH(E)-. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the -Q-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_s$-X-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_s$-O-P-I-J-T type. In another particular embodiment -W- is -NH-CH(E)-, and -Z is a radical of the $-(CH_2)_2$-NR4-P-I-J-T type. In another

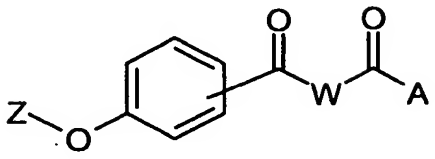
260	3-(4-Benzyloxyphenyl)-2-{4-[(phenylpyridin-2-yl-carbamoyl)methoxy]-benzoylamino}propionic acid; ^{1}H-NMR: 9.92 (d, 1H), 7.62-7.40 (m, 6H), 7.35 (d, 2H), 7.30-7.10 (m, 7H), 7.12 (d, 1H), 6.97 (d, 2H), 6.90 (2H), 6.75 (d, 2H), 5.27 (s, 2H), 4.89 (s 2H), 4.76 (t, 1H), 3.11 (dd, 1H), 3.01 (dd, 1H)
261	3-(4-Benzyloxyphenyl)-2-{4-[(cyclohexylphenylcarbamoyl)methoxy]benzoylamino}propionic acid; MS: 607
262	3-(4-Benzyloxyphenyl)-2-{4-[(*tert*-butylcyclohexylcarbamoyl)methoxy]-benzoylamino}propionic acid; MS: 587
263	3-(4-Benzyloxyphenyl)-2-(4-{[(2-fluorophenyl)thiophen-2-ylmethylcarbamoyl]methoxy}benzoylamino)propionic acid; MS: 639
264	(2*S*)-3-(4-Benzyloxyphenyl)-2-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoylamino}propionic acid; MS: 578
265	(2*S*)-3-((4-Benzyloxybenzyl)-{3-[2-(3-methyl-2-oxo-2*H*-quinoxalin-1-yl)ethoxy]benzoyl}amino)propionic acid; MS: 592

EXAMPLES (Ic) and (Id)

The compounds of formula (Ic) and (Id) shown in Table 18 were synthesized either according to any of methods A to C, starting from compounds of formula (Ib) and the aminic derivatives HNR_2R_3 oR HNR_2OR_1:

CLAIMS

1. A compound of formula (I),



(I)

its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein the central benzene ring may be substituted in *meta*- or *para*-position and,

-A is a radical selected from the group consisting of -OR1, -NR2OR1 and -NR2R3; wherein R1, R2 and R3 independently represent -H or -$(C_1$-$C_4)$-alkyl;

-W- is a biradical selected from the group: -NH-CH(E)-, and -N(D)-CH_2-CH_2-; wherein E is a radical of the -G-I-J-K type and D is a radical of the -G-I'-J-K type where:

-G- is a bond or a -$(CH_2)_{1-4}$- biradical;

-I- is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br,

(C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, this heterocycle being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c) benzene or benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, this bicyclic system being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-J- is a bond or a biradical selected from the following groups:

a) -$(CH_2)_{1-4}$-alkylidene;

b) -O-, and

c) -O-(C_1-C_4)-alkyl-;

-K is a radical selected from the following groups:

a) -H;

b) (C_1-C_4)-alkyl;

c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all of them optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-,

-NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

d) a radical from a five- or six-membered heterocycle containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

e) phenyl or phenyl optionally substituted by one or several radicals independently selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-I'- is a biradical of a cycle selected from the following groups:

a) cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all optionally

substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) a five- or six-membered aromatic heterocycle containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c) benzene substituted by one or several radicals independently selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or

several -OH or -F, (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F phenyl, phenoxy and benzyloxy; and

d) a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-Z is a radical selected from the following groups:

a) -Q-I-J-T wherein

-Q- is a biradical -$(CH_2)_{1-3}$-;

-I- is as defined above;

-J- is as defined above; and

-T is a radical selected from the following groups:

a.a) -H;

a.b) (C_1-C_4)-alkyl;

a.c) a radical from a cycle selected from the following: cyclopropane, cyclobutane, cyclopentane, cyclohexane and cyclohexene, all of them optionally substituted by one or several radicals independently selected

from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

a.d) a radical from a five- or six-membered heterocycle containing from one to three heteroatoms selected from O, S and N, this heterocycle being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

a.e) phenyl or phenyl optionally substituted by one or several radicals independently selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl,

(C_1-C_4)-alkylsulphenyl,
(C_1-C_4)-alkylsulphonyl,
(C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

a.f) a radical from a bicyclic system consisting of a benzene fused with a five- or six-membered ring optionally containing from one to three heteroatoms selected from O, S and N, being this bicyclic system optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

b) $-(CH_2)_s$-X-P-I-J-T wherein

s is 2 or 3;

-X- is selected from the group consisting of -O-, -S-, -SO-, $-SO_2$- and -NR4-, being R4 a radical selected from the group:

b.a) -H;

b.b) (C_1-C_{10})-alkyl;

b.c) cycloalkyl, cycloalkyl-CO-, cycloalkyl-(C_1-C_3)-alkyl and cycloalkyl-(C_1-C_3)-alkanoyl, wherein the cycloalkyl is a five- or six-membered ring optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and -(C_1-C_4)-alkoxyl optionally substituted by one or several OH or F;

b.d) phenyl, phenyl-CO-, phenyl-(C_1-C_3)-alkyl and phenyl-(C_1-C_3)-alkanoyl, being this aromatic ring optionally substituted by one or several radicals selected from -OH, -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

b.e) a heterocycle, heterocycle-CO, heterocycle-(C_1-C_3)-alkyl and heterocycle-(C_1-C_3)-alkanoyl, wherein the

heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocycle optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is a bond or a $-(CH_2)_{1-4}-$ biradical;

-I- is as defined above;

-J- is as defined above; and

-T is a radical as defined above;

c) $-(CH_2)_u$-CO-NR5-P-I-J-T wherein

u is 1 or 2;

-R5 is a radical selected from the group:

c.a) -H;

c.b) (C_1-C_{10})-alkyl;

c.c) cycloalkyl and cycloalkyl-(C_1-C_3)-alkyl, wherein the cycloalkyl is a five- or six-membered ring optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, $-NO_2$, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl,

(C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

c.d) phenyl and phenyl-(C_1-C_3)-alkyl, being this aromatic ring optionally substituted by one or several radicals selected from -OH, -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

c.e) a heterocycle and heterocycle-(C_1-C_3)-alkyl, wherein the heterocycle is a five- or six-membered ring containing from one to three heteroatoms selected from O, S and N, being this heterocyclo optionally substituted by one or several radicals selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally

substituted by one or severalseveral -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F;

-P- is as defined above;

-I- is as defined above;

-J- is as defined above; and

-T is as defined above;

d) -$(CH_2)_s$-NR6R7, wherein s is as defined above, and R6 and R7 together with the N are joined forming a five-, six, or seven-membered cycle optionally containing from one to three additional heteroatoms selected from O, S and N, and that may be fused or substituted by one or two five- or six-membered cycles optionally containing one or several heteroatoms selected from the group composed of O, S and N, all the cycles being optionally substituted by one or several radicals independently selected from -OH, oxo (=O), -CHO, -SH, -NO_2, -CN, -F, -Cl, -Br, (C_1-C_4)-alkanoyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyloxy, (C_1-C_4)-alkylsulphinyl, (C_1-C_4)-alkylsulphenyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-alkyloxy-SO_2-, (C_1-C_4)-alkyl-SO_2O-, -NR2R3, -CONR2R3, (C_1-C_4)-alkyl optionally substituted by one or several -OH or -F, and (C_1-C_4)-alkoxyl optionally substituted by one or several -OH or -F; and

e) -$(CH_2)_u$-CO-NR6R7 wherein u is as defined above, and R6 and R7 are as defined above;

with the proviso that compound of formula (I) is neither of 2-(4-benzyloxybenzoylamino)-3-phenylpropionic acid, 2-[4-(4-methoxybenzyloxy)benzoylamino]-3-phenylpropionic acid, 2-[4-(4-bromobenzyloxy)benzoylamino]-3-phenylpropionic

acid, , cyclopentyl-[4-(2-methylquinolin-4-ylmethoxy)benzoylamino]acetic acid methyl ester, [4-(2-methylquinolin-4-ylmethoxy)benzoylamino](tetrahydropyran-4-yl)acetic acid methyl ester or 2-(4-benzyloxybenzoylamino)-3-biphenyl-4-ylpropionic acid or 2-(4-benzyloxybenzoylamino)-3-(4'-trifluoromethoxybiphenyl-4-yl)propionic acid.

2. The compound according to claim 1, wherein W is -NH-CH(E)-.

3. The compound according to claim 2, wherein -Z is a radical of the -Q-I-J-T type.

4. The compound according to claim 2, wherein -Z is a radical of the $-(CH_2)_s$-X-P-I-J-T type.

5. The compound according to claim 4, wherein -X- is -O-.

6. The compound according to claim 4, wherein s is 2 and -X- is -NR4-.

7. The compound of claim 1, wherein W is $-N(E)-CH_2-CH_2-$.

8. The compound according to claim 7, wherein -Z is a radical of the -Q-I-J-T type.